

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 888

[Docket No. 02P–0294]

Medical Devices; Reclassification of Polymethylmethacrylate (PMMA) Bone Cement

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is announcing that it has reclassified the polymethylmethacrylate (PMMA) bone cement intended for use in arthroplastic procedures of the hip, knee, and other joints for the fixation of polymer or metallic prosthetic implants to living bone from class III to class II (special controls). The agency is also announcing that it has issued an order in the form of a letter to the Orthopedic Surgical Manufacturers Association (OSMA) reclassifying the device. The special control for the device is a guidance document entitled “Class II Special Controls Guidance Document: Polymethylmethacrylate (PMMA) Bone Cement.” The agency is reclassifying this device into class II because special controls, in addition to general controls, would provide reasonable assurance of the safety and effectiveness of the device, and there is sufficient information to establish special controls.

DATES: The reclassification was effective October 14, 1999. The revision of § 888.3027 is effective *[insert date 30 days after date of publication in the **Federal Register**]*.

FOR FURTHER INFORMATION CONTACT: Hany W. Demian, Center for Devices and Radiological Health (HFZ–410), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301–594–2036.

SUPPLEMENTARY INFORMATION:

I. Background

The Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 301 *et. seq.*), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Public Law 94–295), the Safe Medical Devices Act of 1990 (the SMDA) (Public Law 101–629), and the Food and Drug Administration Modernization Act of 1997 (the FDAMA) (Public Law 105–115), established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

The 1976 amendments broadened the definition of “device” in section 201(h) of the act (21 U.S.C. 321(h)) to include certain articles that were once regulated as drugs. Under the 1976 amendments, Congress classified all transitional devices, i.e., those devices previously regulated as new drugs, including the PMMA bone cement, into class III. The legislative history of the SMDA reflects congressional concern that many transitional devices were being overregulated in class III (H. Rept. 808, 101st Cong., 2d sess. 26–27 (1990); S. Rept. 513, 101st Cong., 2d sess. 27 (1990)). Congress amended section 520(l) of the act (21 U.S.C. 360j(l)) to direct FDA to collect certain safety and effectiveness information from the manufacturers of transitional devices still remaining in class III to determine whether the devices should be reclassified into class II (special controls) or class I (general controls). Accordingly, in the **Federal Register** of November 14, 1991 (56 FR 57960), FDA issued an order under section 520(l)(5)(A) of the act, requiring manufacturers of transitional devices, including the PMMA bone cement (21 CFR 888.3027), to submit to FDA a summary of, and a citation to, any information known or otherwise available to them respecting the devices, including adverse safety or effectiveness information which had not been submitted under section 519 of the act (21 U.S.C. 360i). Manufacturers were to submit the summaries and citations to FDA by January 13, 1992. However, because of misunderstandings and uncertainties

regarding the information required by the order, and whether the order applied to certain manufacturers' devices, many transitional class III device manufacturers failed to comply with the reporting requirement by January 13, 1992. Consequently, in the **Federal Register** of March 10, 1992 (57 FR 8462), FDA extended the reporting period to March 31, 1992.

Section 520(l)(5)(B) of the act provides that, after the issuance of an order requiring manufacturers to submit a summary of, and citation to, any information known or otherwise available respecting the devices, but before December 1, 1992, FDA was to publish regulations either leaving transitional class III devices in class III or reclassifying them into class I or II. Subsequently, as permitted by section 520(l)(5)(C) of the act, in the **Federal Register** of November 30, 1992 (57 FR 56586), the agency published a notice extending the period for issuing such regulations until December 1, 1993. Due to limited resources, FDA was unable to publish the regulations before the December 1, 1993, deadline.

II. Recommendation of the Panel

On January 21, 1998, FDA filed the reclassification petition submitted by OSMA, requesting reclassification of the PMMA bone cement from class III to class II. FDA consulted with the Orthopedic and Rehabilitation Devices Panel (the Panel) regarding reclassification of the PMMA bone cement. During an open public meeting on April 28, 1998, the Panel unanimously recommended that FDA reclassify the PMMA bone cement intended for use in arthroplastic procedures of the hip, knee, and other joints for the fixation of polymer or metallic prosthetic implants to living bone from class III to class II. The Panel also recommended that FDA guidance documents, consensus standards, and labeling be the special controls to reasonably assure the safety and effectiveness of the device.

FDA considered the Panel's recommendation and tentatively agreed that the generic type of device, the PMMA bone cement intended for use in arthroplastic procedures of the hip, knee, and other joints for the fixation of polymer or metallic prosthetic implants to living bone, be

reclassified from class III into class II. FDA agreed that guidance documents, consensus standards, and labeling are appropriate special controls for the device.

After reviewing the data in the petition and presented before the Panel, and after considering the Panel's recommendation and the comments, FDA, based on the information set forth, issued an order to the petitioner on October 14, 1999, reclassifying the PMMA bone cement, and substantially equivalent devices of this generic type, from class III to class II with the implementation of special controls.

The special controls listed in the order to the petitioner were the following FDA guidance documents, consensus standards, and labeling:

A. FDA Guidance Documents

1. "Use of International Organization for Standardization (ISO) 10993, 'Biological Evaluation of Medical Devices Part I: Evaluation and Testing',"
2. "510(k) Sterility Review Guidance and Revision of 11/18/94 K90-1,"
3. "Guidance Document for Testing Orthopedic Bone Cement," and
4. "Guidance Document for the Preparation of Premarket Notification (510(k)) Applications for Orthopedic Devices."

B. Consensus Standards

1. American Society for Testing and Material (ASTM) F 451-95 "Standard Specifications for Acrylic Bone Cement,"
2. ASTM D 638-91 "Standard Test Method for Tensile Properties of Plastics,"
3. ASTM D 732-93 "Standard Test Method for Shear Strength of Plastics by Punch Tool,"
4. ASTM D 790-98 "Standard Test Method for Flexural Properties of Unreinforced and Reinforced Plastics and Electrical Insulating Materials,"
5. ASTM D 2990-95 "Standard Tensile, Compressive, and Flexural Creep and Creep Rupture of Plastics,"

6. ASTM E 399–90 “Standard Test Method for Plane-Strain Fracture Toughness of Metallic Materials,”

7. ASTM E 647–95a “Standard Test Method for Measurement of Fatigue Crack Growth Rates,” and

8. International Organization for Standardization (ISO) 5833:1992 “Implants for surgery—Acrylic resin cements.”

C. Labeling

1. Contraindication

Do not use PMMA bone cement in the presence of active or incompletely treated infection that could involve the site where the device will be implanted.

2. Warnings

a. Adverse cardiovascular reactions, including hypotension, hypoxaemia, cardiac arrhythmia, bronchospasm, cardiac arrest, myocardial infarction, pulmonary embolism, cerebrovascular accident, and possible death: Hypotensive reactions can occur between 10 and 165 seconds after application of the PMMA bone cement and can last for 30 seconds to 5 or more minutes. Some hypotensive reactions have progressed to cardiac arrest. The blood pressure of patients should be monitored carefully during and immediately following the application of the PMMA bone cement. In addition, overpressurization of the PMMA bone cement should be avoided during insertion of the PMMA bone cement and implant in order to minimize the occurrence of pulmonary embolism.

b. Surgeon training and experience: The surgeon should be thoroughly familiar with the properties, handling characteristics and application of the PMMA bone cement. Because the handling and curing characteristics of this cement vary with temperature and mixing technique, they are best determined by the surgeon’s actual experience.

c. Device volatility and flammability and electrocautery devices: The operating room should be adequately ventilated to eliminate monomer vapors. Ignition of monomer vapors caused by the use of electrocautery devices in surgical sites near freshly implanted bone cement has been reported.

d. Irritation of the respiratory tract, eyes, and the liver: Caution should be exercised during the mixing of the liquid and powder components of the PMMA bone cement to prevent excessive exposure to the concentrated vapors of liquid monomer, which may produce irritation of the respiratory tract, eyes, and possibly the liver. Personnel wearing contact lenses should not mix PMMA bone cement or be near the mixing of the PMMA bone cement.

3. Precautions

a. Contact dermatitis: The liquid monomer has caused contact dermatitis in those handling and mixing PMMA bone cement. Strict adherence to the instructions for mixing the powder and liquid components may reduce the incidence of contact dermatitis.

b. Hypersensitivity reactions: The liquid component of PMMA bone cement is a powerful lipid solvent. It should not contact rubber or latex gloves. Double gloving and strict adherence to the mixing instructions may diminish the possibility of hypersensitivity reactions. The mixed PMMA bone cement should not contact the gloved hand until the cement has acquired the consistency of dough, about 1 to 2 minutes after mixing.

c. Inadequate postoperative fixation: Inadequate fixation or unanticipated postoperative events may affect the PMMA bone cement-bone interface and lead to micromotion of cement against the bone surface. A fibrous tissue layer may develop between the PMMA bone cement and the bone that may cause loosening of the prosthesis. Thus, continued, periodic followup is advised for all patients.

d. Exothermic reaction: Polymerization of the PMMA bone cement is an exothermic reaction that occurs while the PMMA bone cement is hardening *in situ*. The released heat may damage bone or other tissue adjacent to the implant.

e. Extrusion: Extrusion of the PMMA bone cement beyond the region of its intended application may occur resulting in the following complications: Hematuria, dysuria, bladder fistula, delayed sciatic nerve entrapment from extrusion of the bone cement beyond the region of its intended application, local neuropathy, local vascular erosion and occlusion, and intestinal obstruction because of adhesions and stricture of the ileum from the heat released during the exothermic polymerization.

f. Use in pregnant women and children: The safety and effectiveness of the PMMA bone cement in pregnant women and in children is not established.

g. Expiration dating: PMMA bone cement should not be used after the expiration date because the effectiveness of the device may be compromised.

h. Disposal: Because of the volatility and flammability of the liquid monomer of the PMMA bone cement, the liquid monomer should be evaporated in a well-ventilated hood or absorbed by an inert material and transferred into a suitable container (one that does not react with the PMMA bone cement) for disposal.

4. Adverse Events

a. Serious adverse events, some with fatal outcome, associated with the use of the PMMA bone cement include myocardial infarction, cardiac arrest, cerebrovascular accident, and pulmonary embolism.

b. The most frequent adverse reactions associated with the use of PMMA bone cement are transitory decreased blood pressure, elevated serum gamma-glutamyl-transpeptidase (GGTP) up to 10 days postoperation, thrombophlebitis, hemorrhage and hematoma, pain and/or loss of function, loosening or displacement of the prosthesis, superficial or deep wound infection, trochanteric bursitis, short-term cardiac conduction irregularities, heterotopic new bone formation, and trochanteric separation.

c. Other potential adverse events associated with the use of PMMA bone cement include allergic pyrexia, hematuria, dysuria, bladder fistula, delayed sciatic nerve entrapment from extrusion

of the bone cement beyond the region of its intended application, local neuropathy, local vascular erosion and occlusion, intestinal obstruction because of adhesions and stricture of the ileum from the heat released during the exothermic polymerization.

FDA incorporated the four FDA guidance documents, eight consensus standards, and labeling into a class II special controls guidance entitled “Class II Special Controls Guidance Document: Polymethylmethacrylate (PMMA) Bone Cement” that issued on August 2, 2001. The guidance document also referenced updated versions of six of the eight consensus standards listed as special controls in the reclassification order. FDA has further revised the guidance document to include the risk to health of polymerization setting problems and to clarify the warnings, precautions, and adverse reactions sections of the labeling. This class II special controls guidance document, is now the special control for this generic device.

Accordingly, as required by 21 CFR 860.136(b)(6) of the regulations, FDA is announcing the reclassification of the generic the PMMA bone cement intended for use in arthroplastic procedures of the hip, knee, and other joints for the fixation of polymer or metallic prosthetic implants to living bone from class III into class II.

III. Access to Special Controls

Persons interested in obtaining a copy of “Class II Special Controls Guidance Document: Polymethylmethacrylate (PMMA) Bone Cement” may do so using the Internet. The Center for Devices and Radiological Health (CDRH) maintains an entry on the Internet for easy access to information including text, graphics, and files that may be downloaded to a personal computer with access to the Internet. The CDRH home page may be accessed at <http://www.fda.gov/cdrh>. Guidance documents are also available from the Division of Small Manufacturers, International, and Consumer Assistance (DSMICA) (HFZ-220), Food and Drug Administration, Center for Devices and Radiological Health, 1350 Piccard Dr., Rockville, MD 20850. In order to receive the guidance document via your fax machine call the CDRH Facts-On-Demand (FOD) system at 800-899-0381 or 301-827-0111 from a touch-tone telephone. Press 1 to enter the system and

enter the document number (668) followed by the pound sign (#). Follow the remaining voice prompts to complete your request.

IV. Environmental Impact

The agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104-121)), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4)). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive order. In addition, the final rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Reclassification of the device from class III to class II will relieve all manufacturers of the device of the cost of complying with the premarket approval requirements in section 515 of the act. Because reclassification will reduce regulatory costs with respect to this device, it will impose no significant economic impact on any small entities, and it may permit small potential competitors to enter the marketplace by lowering their costs. The agency, therefore, certifies that this rule will not have a significant economic impact on a substantial number of small entities. In addition, this rule will not impose costs of \$100

million or more on either the private sector or State, local, and tribal governments in the aggregate, and therefore a summary statement or analysis under section 202(a) of the Unfunded Mandates Reform Act of 1995 is not required.

VI. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, or on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VII. Paperwork Reduction Act of 1995

The premarket notification information collections addressed in the guidance have been approved by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) under OMB control number 0910–0120. The labeling provisions addressed in the guidance have been approved by OMB under the PRA under OMB control number 0910–0485.

List of Subjects in 21 CFR Part 888

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 888 is amended as follows:

PART 888—ORTHOPEDIC DEVICES

1. The authority citation for 21 CFR part 888 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Section 888.3027 is revised to read as follows:

§ 888.3027 Polymethylmethacrylate (PMMA) bone cement.

(a) *Identification.* Polymethylmethacrylate (PMMA) bone cement is a device intended to be implanted that is made from methylmethacrylate, polymethylmethacrylate, esters of methacrylic acid, or copolymers containing polymethylmethacrylate and polystyrene. The device is intended for use in arthroplastic procedures of the hip, knee, and other joints for the fixation of polymer or metallic prosthetic implants to living bone.

(b) *Classification.* Class II (special controls). The special control for this device is the FDA guidance document entitled “Class II Special Controls Guidance Document: Polymethylmethacrylate (PMMA) Bone Cement.”

Dated: July 5, 2002.

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Deputy Director, Center for Devices and Radiological Health.

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